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(54) **Pharmaceutical composition for use in treatment of diabetes**

(57) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mecha-

nism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

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Description

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer in the mechanism of action.

BACKGROUND OF THE INVENTION

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed. Accordingly a variety of drugs having new mechanisms of action have appeared one after another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Fujita et al., Diabetes, 32, 804-810, 1983, JP-A S55(1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and the risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-045, thiazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

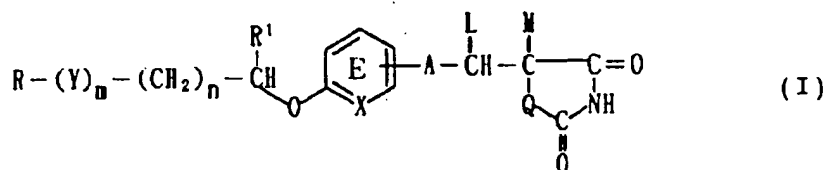
Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

In view of the above state of the art, the inventors of the present invention did much research to develop antidiabetics which would not virtually cause adverse reactions even on long-term administration and could be effective for a large cohort of the diabetic population. As a consequence, they discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

- 1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α -glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;
- 2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a compound represented by the formula:



wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group repre-

5 sented by $-\text{CO}-$, $-\text{CH}(\text{OH})-$ or $-\text{NR}^3-$ (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N ; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent

hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is pioglitazone;

4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination

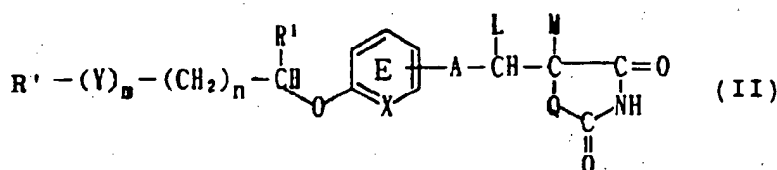
with an α -glucosidase inhibitor;

5) Pharmaceutical composition according to 4), wherein the α -glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α -glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

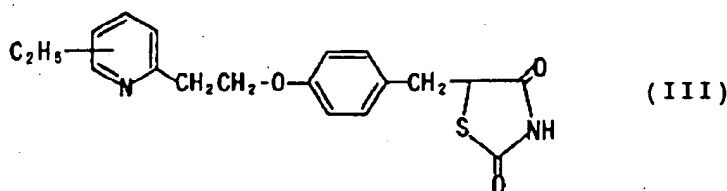
8) Pharmaceutical composition which comprises a compound represented by the formula:



25 wherein R^1 represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by $-\text{CO}-$, $-\text{CH}(\text{OH})-$ or $-\text{NR}^3-$ (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N ; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent

hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R^1 does not represent benzopyranyl group when m and n are 0, X represents CH , A represents a bond, Q represents sulfur atom, R^1 , L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:



45 10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

55 The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R, mention is made of aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C₁₋₈ saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C₂₋₈ unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptyne and 1-octyne.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C₃₋₇ saturated alicyclic hydrocarbon groups (e.g. cycloalkyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C₅₋₇ unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkylalkyl group, cycloalkenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C₇₋₉ phenylalkyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C₁₁₋₁₃ naphthylalkyl as exemplified by α -naphthylmethyl, α -naphthylethyl, β -naphthylmethyl and β -naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α -naphthyl, β -naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may optionally have 1 to 5, preferably 1 to 3 substituents at any substitutable positions. Examples of such substituents include aliphatic hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C₁₋₁₅ straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkenyl group, and alkynyl group.

Preferable examples of the alkyl group include C₁₋₁₀ alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl group include C₂₋₁₀ alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group include C₂₋₁₀ alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C₃₋₁₂ saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkyl group include C₃₋₁₀ cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C₃₋₁₀ cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C₄₋₁₀ cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C₆₋₁₄ aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolyl, quinoxalinyl, phthalazinyl, naphthylidyl, purinyl, pteridinyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenathrolinyl, indoliziny, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholyl, thiomorpholyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group, C₂₋₁₀ alkynyl group, aromatic group, heterocyclic group and C₁₋₁₀ acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenyl-amino, acetylamino, propionylamino, benzoylamino and nicotinoylamino).

As the acyl group, mention is made of C₁₋₁₃ acyl groups such as C₁₋₁₀ alkanoyl group, C₃₋₁₀ alkenoyl group, C₄₋₁₀ cycloalkanoyl group, C₄₋₁₀ cycloalkenoyl group and C₆₋₁₂ aromatic carbonyl group.

Preferable examples of the C₁₋₁₀ alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C₃₋₁₀ alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C₄₋₁₀ cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C₄₋₁₀ cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C₆₋₁₂ aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C₁₋₃ alkyl group, C₁₋₃ alkoxy group, halogen atom (e.g. chlorine, fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C₁₋₁₀ alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C₃₋₁₀ cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C₂₋₁₀ alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyl and 3-hexenyl. Preferable examples of the cycloalkenyloxy group include C₃₋₁₀ cycloalkenyloxy groups such as 2-cyclopentenyl and 2-cyclohexenyl. Preferable examples of the aralkyloxy group include C₇₋₁₀ aryloxy groups such as phenyl-C₁₋₄alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group include C₂₋₁₃ acyloxy group, more preferably C₂₋₄ alkanoyloxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C₆₋₁₄ aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of the alkylthio group include C₁₋₁₀ alkylthio groups such as methylthio, ethylthio, propylthio,

isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalkylthio group include C₃₋₁₀ cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C₂₋₁₀ alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio and 3-hexenylthio. Preferable examples of the cycloalkenylthio group include C₃₋₁₀ cycloalkenylthio groups such as 2-cyclopentenylthio and 2-cyclohexenylthio. Preferable examples of the aralkylthio include C₇₋₁₀ aralkylthio groups such as phenyl-C₁₋₄alkylthio (e.g. benzylthio and phenethylthio). Preferable examples of the acylthio group include C₂₋₁₃ acylthio group, more preferably C₂₋₄ alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio and isobutyrylthio).

Preferable examples of the arylthio group include C₆₋₁₄ arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenylthio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxycarbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C₂₋₅ alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl group include C₆₋₁₀ aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C₇₋₁₅ aryloxycarbonyl groups such as phenoxycarbonyl and p-toloyloxycarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C₁₋₁₀ alkyl groups, aromatic heterocyclic groups and C₆₋₁₄ aryl groups are preferable, and C₁₋₃ alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C₁₋₆ alkyl groups, C₂₋₆ alkenyl groups, C₂₋₆ alkynyl groups, C₃₋₇ cycloalkyl groups, C₆₋₁₄ aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C₇₋₉ aralkyl groups, amino group, N-mono-C₁₋₄ alkylamino groups, N,N-di-C₁₋₄ alkylamino groups, C₂₋₈ acylamino groups (e.g. acetylamino, propionylamino and benzoylamino), amidino group, C₂₋₈ acyl group (e.g. C₂₋₈ alkanoyl groups), carbamoyl group, N-mono-C₁₋₄ alkyl carbamoyl groups, N,N-di-C₁₋₄ alkyl carbamoyl groups, sulfamoyl group, N-mono-C₁₋₄ alkyl sulfamoyl groups, N,N-di-C₁₋₄ alkyl sulfamoyl groups, C₂₋₈ alkoxycarbonyl groups, hydroxyl group, C₁₋₄ alkoxy groups, C₂₋₅ alkenyloxy groups, C₃₋₇ cycloalkyloxy groups, C₇₋₉ aralkyloxy groups, C₆₋₁₄ aryloxy groups, mercapto group, C₁₋₄ alkylthio groups, C₇₋₉ aralkylthio groups, C₆₋₁₄ arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In the formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl group which is optionally substituted by 1 to 3 substituents selected from C₁₋₃ alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are O; X represents CH; A represents a bond; Q represents sulfur atom; R¹, L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents -CO-, -CH(OH)- or -NR³- (wherein R³ represents an optionally substituted alkyl group), preferably -CH(OH)- or -NR³-. As the alkyl group in the optionally substituted alkyl group represented by R³, mention is made of, for example, C₁₋₄ alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C₁₋₄ alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C₁₋₄ acyl groups (e.g. formyl, acetyl and propionyl).

The symbol m is 0 or 1, preferably 0.

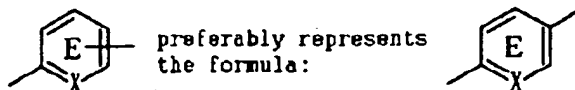
The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

In the formulae (I) and (II), A represents a bond or a C₁₋₇ divalent aliphatic hydrocarbon group. The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. -CH₂-, -CH(CH₃)-, -(CH₂)₂-, -CH(C₂H₅)-, -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆- and -(CH₂)₇-] and unsaturated ones [e.g. -CH=CH-, -C(CH₃)=CH-, -CH=CH-CH₂-, -C(C₂H₅)=CH-, -CH₂-CH=CH-CH₂-, -CH₂-CH₂-CH=CH-CH₂-, -CH=CH-CH=CH-CH₂- and -CH=CH-CH=CH-CH=CH-CH₂-]. A is preferably a bond or C₁₋₄ divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or -(CH₂)₂-.

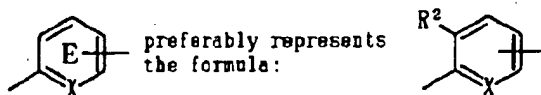
As the alkyl group represented by R¹, substantially the same one as the alkyl group in the above-mentioned R³. R¹ is preferably hydrogen atom.

In the formulae (I) and (II), the partial formula:



Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

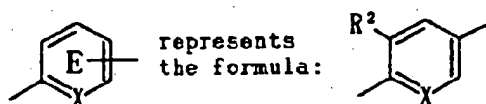
As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2 , mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formulae (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

In the compounds wherein L and M are combined with each other to form a bond, there exist (E)- and (Z)-isomers relative to the double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)- and (S)-optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)- and (S)- optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those in which R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $-(CH_2)_2-$; R^1 is hydrogen atom; ring E, namely the partial formula:



and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2-(6-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione;

(2) (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and
(3) 5-[4-[2-(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone/CS-045).

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a salt thereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61(1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269(EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-{3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl}phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768);

5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[[2-(naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-{2-(methyl-2-pyridylamino)ethoxy}phenyl]methyl]-2,4-thiazolidinedione (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α -glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

α -Glucosidase inhibitors are drugs which inhibit digestive enzymes such as amylase, maltase, α -dextrinase, sucrase, etc. to retard digestion of starch and sugars. Examples of the α -glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name: voglibose), miglitol, etc. with preference given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limiting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluorospiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat);

3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestat);

6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860);

zopolrestat; sorbinil; and

1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutaryl CoA (HMG-CoA) reductase.

Examples of the statin compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene.

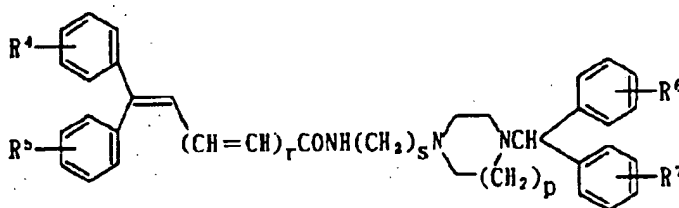
Examples of the squalene synthesis inhibitors include (S)- α -[Bis[2,2-dimethyl-1-oxopropoxy)methoxy]phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase.

Examples of the fibrate compounds include bezafibrate, beclobate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144 and represented by the formula:



wherein R^4 , R^5 , R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0-2; s is 2-4; p is 1-2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl)methyl-1-piperazinyl]ethyl]-7,7-diphenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritol; antioxidants such as probucol; and ionexchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes.

Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moxeltopril, perindopril, quinapril, spirapril, temocapril,trandolapril, etc.

In the present invention, especially preferred is the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α -glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglitazone, and the α -glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the SU include tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybutiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolycyclamide, etc.

Insulin secretion enhancers include N-[4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalanine (AY-4166); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isindoliny carbonyl)propionate dihydrate (KAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or porcine pancreas and human insulin preparations synthesized by genetic engineering techniques typically using *Escherichia coli* or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting, intermediate-acting, and long-acting, these types of preparations can be selectively administered according to the

patient's condition.

In the present invention, especially preferred is the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an α -glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrin compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α -starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonicizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage-form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cottonseed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with

reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg body weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglitazone) which is the insulin sensitivity enhancer and voglibose which is an α -glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.0001 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weight part of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of the present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic Wistar fatty rats with genetical obesity, administration of these active components in combination resulted in marked improvements in both hyperglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of the invention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

Working Example 1

Capsules

| | |
|--------------------------------|---------|
| (1) Pioglitazone hydrochloride | 30 mg |
| (2) Voglibose | 0.2 mg |
| (3) Lactose | 60 mg |
| (4) Microcrystalline cellulose | 79.8 mg |
| (5) Magnesium stearate | 10 mg |
| Total | 180 mg |

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

Working Example 2

Tablets

| | |
|--------------------------------|-------|
| (1) Pioglitazone hydrochloride | 10 mg |
|--------------------------------|-------|

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(continued)

| | |
|----------------------------|---------------------|
| (2) Glibenclamide | 1.25 mg |
| (3) Lactose | 86.25 mg |
| (4) Corn starch | 20 mg |
| (5) Polyethylene glycol | 2.5 mg |
| (6) Hydroxypropylcellulose | 4 mg |
| (7) Carmellose calcium | 5.5 mg |
| (8) Magnesium stearate | 0.5 mg |
| | 130 mg (per tablet) |

The whole amounts of (1), (2), (3), (4), and (5), 2/3 amounts of (6) and (7), and 1/2 amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

Working Example 3

Capsules

| | |
|--------------------------------|--------------|
| (1) Pioglitazone hydrochloride | 10 mg |
| (2) Epalrestat | 50 mg |
| (3) Lactose | 55 mg |
| (4) Microcrystalline cellulose | 55 mg |
| (5) Magnesium stearate | 10 mg |
| | Total 180 mg |

The whole amounts of (1), (2), (3) and (4) and 1/2 amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 divided doses.

Experimental Example 1

Effect of pioglitazone hydrochloride in combination with α -glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 14-19 weeks were divided into 4 groups of 5-6, and pioglitazone hydrochloride (1 mg/kg body wt./day, p.o.) and/or voglibose (an α -glucosidase inhibitor) (0.31 mg/kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was administered for 14 days. The blood was then collected from the tail vein and the plasma glucose and hemoglobin A₁ were determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean \pm standard deviation for each group (n=5-6) and analyzed by Dunnett's test, which are shown in Table 1. The 1% level of significance was used.

[Table 1]

| Group | Plasma glucose (mg/dl) | Hemoglobin A ₁ (%) |
|--------------------------|------------------------|-------------------------------|
| Control | 345 \pm 29 | 5.7 \pm 0.4 |
| Pioglitazone | 215 \pm 50* | 5.2 \pm 0.3 |
| Voglibose | 326 \pm 46 | 6.0 \pm 0.6 |
| Pioglitazone + voglibose | 114 \pm 23* | 4.5 \pm 0.4* |

*: P<0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A₁ levels were remarkably lowered by

combined administration of pioglitazone and voglibose as compared with the administration of either drug alone.

Experimental Example 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 13-14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o.) was administered for 7 days. Following an overnight fast, the oral glucose loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean \pm SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

[Table 2]

| Group | Plasma glucose (mg/dl) | | |
|------------------------------|------------------------|---------------|---------------|
| | 0 min. | 120 min. | 240 min. |
| Control | 119 \pm 9 | 241 \pm 58 | 137 \pm 10 |
| Pioglitazone | 102 \pm 12 | 136 \pm 17* | 102 \pm 9* |
| Glibenclamide | 118 \pm 12 | 222 \pm 61 | 106 \pm 24* |
| Pioglitazone + glibenclamide | 108 \pm 3 | 86 \pm 10* | 60 \pm 5* |

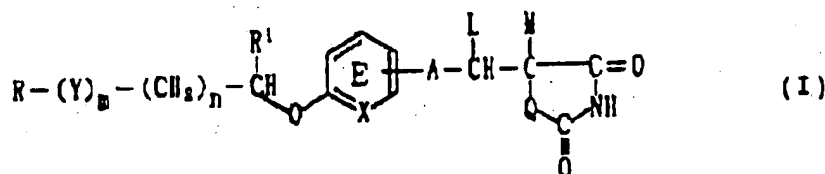
*: P<0.01 vs. control group

It is apparent from Table 2 that the increase of blood sugar following glucose loading was remarkably inhibited by the combined administration of pioglitazone and glibenclamide as compared with the administration of either drug alone.

The pharmaceutical composition of the present invention shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route, dosage, etc. according to clinical status, stable hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

Claims

1. Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α -glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.
2. Pharmaceutical composition according to Claim 1, wherein the insulin sensitivity enhancer is a compound represented by the formula:



wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by -CO-, -CH(OH)- or -NR³- (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C₁₋₇ divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R¹ represents hydrogen atom or an alkyl group; ring E may optionally have further 1 to 4 substituents, and the substituents may optionally be combined with R¹ to form a ring; L and M respectively

represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmaceutically acceptable salt thereof.

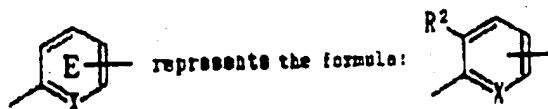
3. Pharmaceutical composition according to claim 1, wherein R is an optionally substituted heterocyclic group.

4. Pharmaceutical composition according to claim 1, wherein m is 0.

5. Pharmaceutical composition according to claim 1, wherein X is CH.

6. Pharmaceutical composition according to claim 1, wherein R¹ is hydrogen atom.

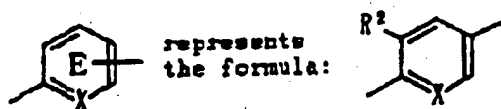
7. Pharmaceutical composition according to claim 1, wherein the partial formula:



20 wherein R² represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

8. Pharmaceutical composition according to claim 1, wherein L and M are hydrogen atom.

9. Pharmaceutical composition according to claim 1, wherein R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C₁₋₃ alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or -(CH₂)₂-; R¹ is hydrogen atom; the partial formula:



35 and R² is hydrogen atom or C₁₋₄ alkoxy group; and L and M are both hydrogen atom.

10. Pharmaceutical composition according to Claim 2, wherein the compound represented by the formula (I) is pioglitazone.

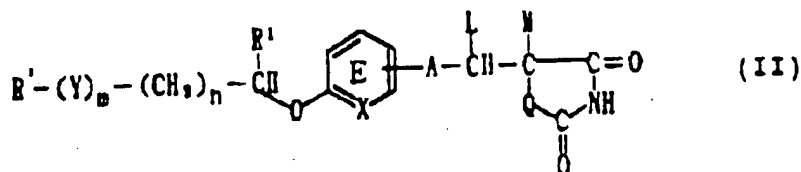
11. Pharmaceutical composition according to Claim 1, which comprises an insulin sensitivity enhancer in combination with an α -glucosidase inhibitor.

12. Pharmaceutical composition according to Claim 11, wherein the α -glucosidase inhibitor is voglibose.

13. Pharmaceutical composition according to Claim 11, wherein the insulin sensitivity enhancer is pioglitazone and the α -glucosidase inhibitor is voglibose.

14. Pharmaceutical composition according to claim 1, which is for prophylaxis or treatment of diabetes.

15. Pharmaceutical composition which comprises a compound represented by the formula:



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by -CO-, -CH(OH)- or -NR³- (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C₁₋₇ divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R¹ represents hydrogen atom or an alkyl group; ring E may optionally have further 1 to 4 substituents, and the substituents may optionally be combined with R¹ to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are O, X represents CH, A represents a bond, Q represents sulfur atom, R¹, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation.

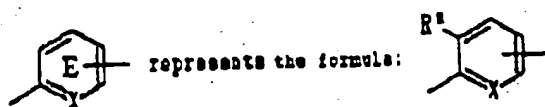
16. Pharmaceutical composition according to claim 15, wherein R' is an optionally substituted heterocyclic group.

17. Pharmaceutical composition according to claim 15, wherein m is 0.

18. Pharmaceutical composition according to claim 15, wherein X is CH.

19. Pharmaceutical composition according to claim 15, wherein R¹ is hydrogen atom.

20. Pharmaceutical composition according to claim 15, wherein the partial formula:



wherein R² represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

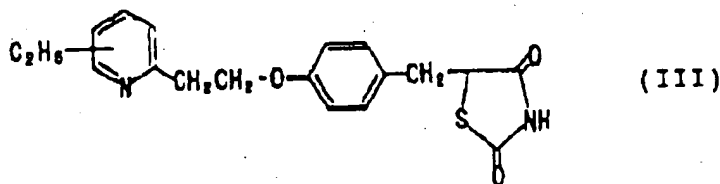
21. Pharmaceutical composition according to claim 15, wherein L and M are hydrogen atom.

22. Pharmaceutical composition according to claim 15, wherein R' is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C₁₋₃ alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or -(CH₂)₂-; R¹ is hydrogen atoms the partial formula:



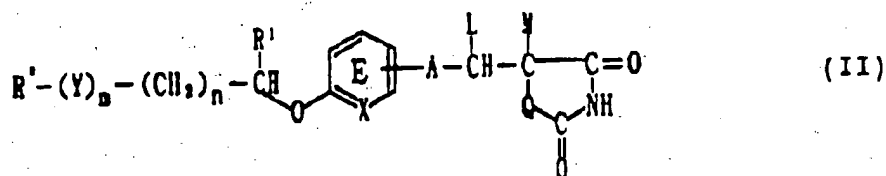
and R² is hydrogen atom or C₁₋₄ alkoxy group; and L and M are both hydrogen atom.

23. Pharmaceutical composition according to Claim 15, wherein the compound represented by the formula (II) is the compound represented by the formula:



24. Pharmaceutical composition according to Claim 15, wherein the compound represented by the formula (II) is pioglitazone.

25. Pharmaceutical composition according to Claim 15, wherein the insulin secretion enhancer is glibenclamide.
26. Pharmaceutical composition according to Claim 15, wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide.
27. Pharmaceutical composition according to Claim 15, which is for prophylaxis or treatment of diabetes.
28. Use of an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α -glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor for the manufacture of a pharmaceutical composition for treating diabetes.
29. Use of a compound represented by the formula:



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by -CO-, -CH(OH)- or -NR³- (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C₁₋₇ divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R¹ represents hydrogen atom or an alkyl group; ring E may optionally have further 1 to 4 substituents, and the substituents may optionally be combined with R¹ to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are 0, X represents CH, A represents a bond, Q represents sulfur atom, R¹, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof, in combination with an insulin secretion enhancer and/or an insulin preparation for the manufacture of a pharmaceutical composition for treating diabetes.

(19)



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(54) **Pharmaceutical composition for use in treatment of diabetes**

(57) Pharmaceutical composition which comprises
an insulin sensitivity enhancer in combination with other
antidiabetics differing from the enhancer in the mecha-

nism of action, which shows a potent depressive effect
on diabetic hyperglycemia and is useful for prophylaxis
and treatment of diabetes.

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EUROPEAN SEARCH REPORT

Application Number
EP 96 30 4570

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|---|---|--|---|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
| P,X | AMERICAN JOURNAL OF PHYSIOLOGY, vol. 269, no. 4, part 1, October 1995, USA, pages E786-E792, XP000600693 STURIS ET AL: "PREVENTION OF DIABETES DOES NOT COMPLETELY PREVENT INSULIN SECRETORY DEFECTS IN THE ZDF RAT" * abstract * | 1 | A61K31/41 //(A61K31/41, A61K31:00) |
| P,Y | DIABETES CARE, vol. 18, no. 8, August 1995, USA, pages 1215-1219, XP000600655 BLOOMSGARDEN: "AMERICAN DIABETES ASSOCIATION SCIENTIFIC SESSIONS, 1995: NON-INSULIN- DEPENDENT DIABETES MELLITUS" * page 1216, middle column, paragraph 2 * | 1 | TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K |
| Y | EXPERT OPIN. INVEST. DRUGS, vol. 4, no. 12, 1995, BRITAIN, pages 1299-1309, XP000600699 WHITCOMB ET AL: "THIAZOLIDINEDIONES" * page 1304, left-hand column, paragraph 1 - page 1305, left-hand column, paragraph 1 * | 1 | |
| A | J. THE DIABETIC ASSOCIATION OF INDIA, vol. 34, no. 3-4, 1994, INDIA, pages 59-61, XP000600694 NIHALANI ET AL: "NEWER ORAL HYPOGLYCEAMIC (ANTIDIABETIC) AGENTS" * page 60, left-hand column, paragraph 1 * | 1 | |
| A | WO 93 03724 A (UPJOHN CO) 4 March 1993 * abstract * | 1 | |
| The present search report has been drawn up for all claims | | | |
| Place of search MUNICH | | Date of completion of the search 1 October 1996 | Examiner Herrera, S |
| CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document | | T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document | |

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claims:
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

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- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respects of which search fees have been paid, namely claims:
- ☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims: mentioned in item 1.



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LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claim 1 (partly): Insulin sensitivity enhancer + glucosidase inhibitor (searched)
2. Claim 1 (partly): Insulin sensitivity enhancer + aldose reductase inhibitor
3. Claim 1 (partly): Insulin sensitivity enhancer + biguanide
4. Claim 1 (partly): Insulin sensitivity enhancer + statin compound
5. Claim 1 (partly): Insulin sensitivity enhancer + squalene synthesis inhibitor
6. Claim 1 (partly): Insulin sensitivity enhancer + fibrate compound
7. Claim 1 (partly): Insulin sensitivity enhancer + LDL catabolism enhancer
8. Claim 1 (partly): Insulin sensitivity enhancer + angiotensin converting enzyme
9. Claim 15 (partly): Insulin sensitivity enhancer according to formula II + insulin secretion enhancer
10. Claim 15 (partly): Insulin sensitivity enhancer according to formula II + insulin preparation

No common concept can be seen between the combinations with the different antidiabetes drugs, especially since the general concept (combining insulin sensitivity enhancer and an other antidiabetes drug having a different mechanism) is already known from the documents cited in the description